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CASE REPORT

Meningeal seeding from glioblastoma multiforme treated with radiotherapy and temozolomide

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Summary Extracranial and meningeal seeding of glioblastoma multiforme is rare. We report herein a case of glioblastoma in a 41-year-old man who underwent surgical resection, concomitant chemoradiotherapy (CCRT) and seven courses of adjuvant chemotherapy with temozolomide. The patient then complained of intermittent severe lower back pain and gait disturbance. Imaging studies demonstrated that although the intracranial residual tumors were well-controlled by the treatment, meningeal seeding involving the brainstem and spinal cord was present. The patient died 2 months after the diagnosis of spinal seeding. This case illustrates the need for consideration of extracranial metastasis if a patient is symptomatic, even if the intracranial tumor appears responsive to treatment. We suggested that the prophylactic craniospinal irradiation may be considered in patients at high risk of meningeal seeding immediately after surgery.

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1. Introduction

Glioblastoma multiforme (GBM) is the most malignant primary brain tumor, for which current standard treatment includes surgical resection, concomitant chemo-radiotherapy with temozolomide (TMZ), and adjuvant chemotherapy for 6—12 cycles. Extracranial seeding of GBM is very rare, especially when the tumor is well-controlled at the primary site. Whether temozolomide chemotherapy can prevent meningeal seeding is not conclusive. We report herein the case of a patient who responded to standard treatment but was diagnosed with meningeal seeding.

2. Case report

A 41-year-old male patient with an unremarkable past medical history presented with blurred vision, intermittent headache, and low-grade fever and was admitted to our hospital. Neurological examination revealed homonymous right hemianopsia. Hemogram, blood chemistry, and urine laboratory data were normal, with the exception of leukocytosis [White blood cell (WBC), 12.4 $\times$ 10^9/L]. Head computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated a well-enhanced mass lesion in the left parieto-occipital lobe with marked perifocal brain edema, which compressed lateral ventricles, and another smaller lesion located anterior to the main mass (Fig. 1A and B). The patient underwent a craniotomy and partial tumor excision, and the satellite lesion was left untouched. Pathological examination of the tumor identified it as GBM. The methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) promoter in the GBM sample was analyzed using methylation-specific PCR, and the MGMT promoter was found to be unmethylated.

After the operation, the patient recovered uneventfully, with the exception of the persistence of a visual field defect. Two weeks after the surgery, he received concomitant chemoradiotherapy (CCRT) with TMZ (75 mg/m^2/day) and external beam X-ray irradiation therapy (60 Gy/2 Gy/fraction), which was tolerated well. Adjuvant chemotherapy with TMZ (200 mg/m^2/day) for 5 days every 4 weeks was subsequently administered. MRI was performed at 3-month intervals and showed no evidence of tumor progression, and the patient returned to work as an engineer 3 months after diagnosis. After the 7th cycle of adjuvant chemotherapy, he complained of intermittent severe lower back pain and gait disturbance. Neurological examination revealed hyperreflexia of the bilateral knee and ankle jerks, and positive cerebellar signs. There was no urinary retention or incontinence. Subsequent MRI revealed no progression of the intracranial tumors, but marked meningeal seeding involving the entire spinal cord and brainstem was observed (Figs. 2 and 3). Lumbar puncture was performed and the cerebrospinal fluid (CSF) cytology demonstrated atypical neoplastic cells with enlarged nuclei and abundant cytoplasm (Fig. 4). CSF examination revealed mild pleiocytosis (21 WBCs/mm^3 with a lymphocyte:monocyte:neutrophil

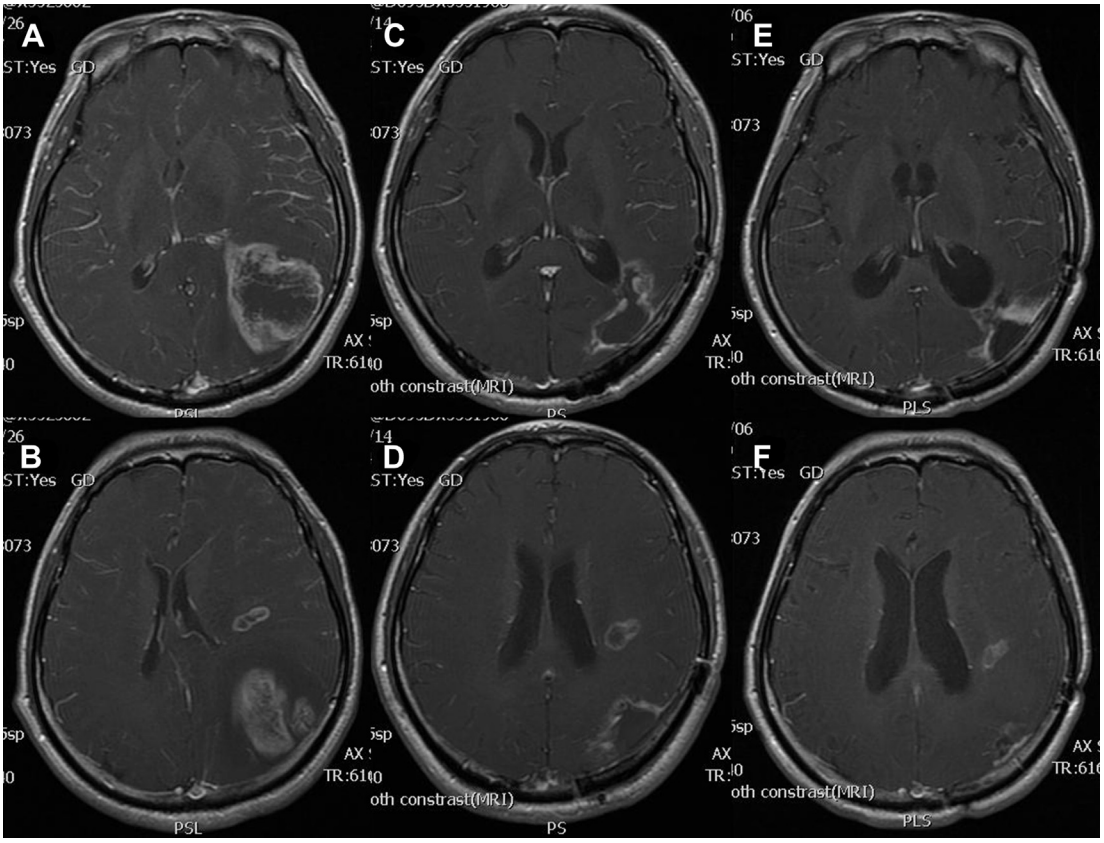

Figure 1 Gadolinium-enhanced axial T1-weighted MRI showing the intracranial tumors prior to surgery (A, B), after CCRT and 5-month adjuvant chemotherapy (C, D), and after spinal seeding had been diagnosed (E, F).

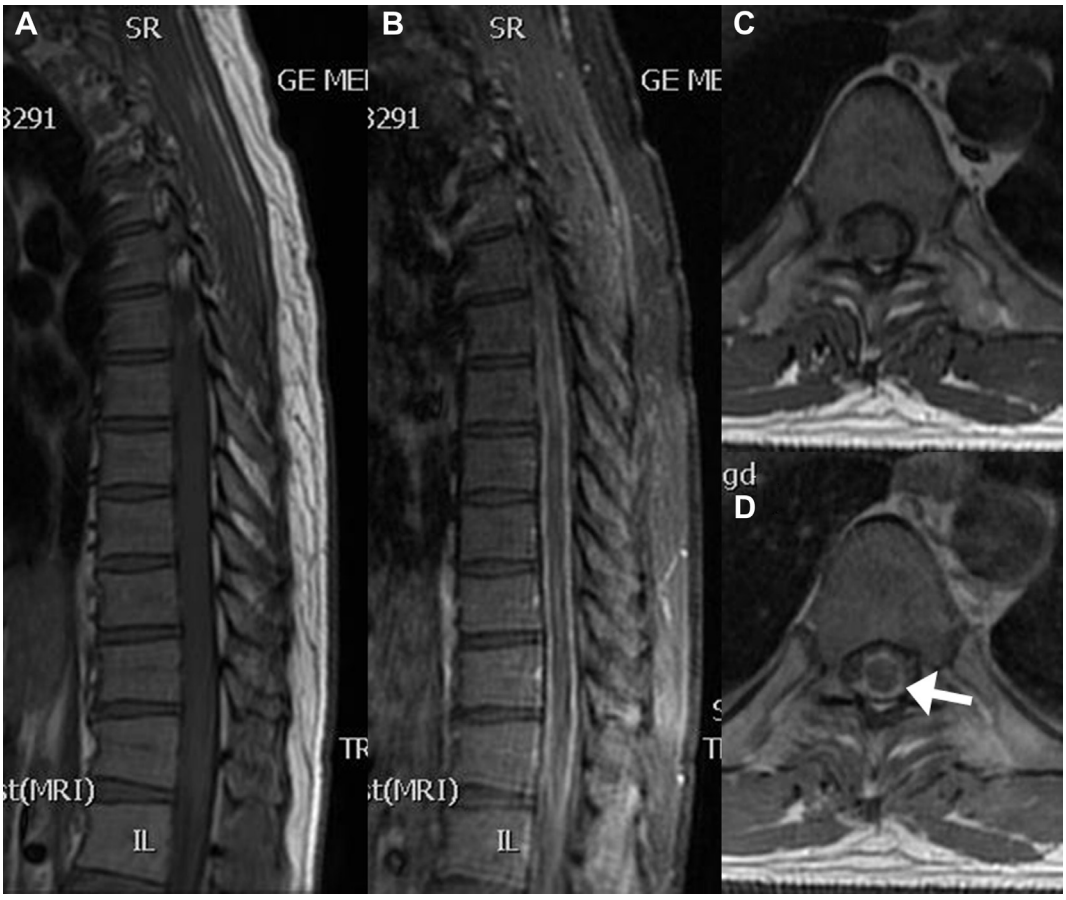

Figure 2 Pre- (A, C) and postcontrast (B, D) T1-weighted MR images of the thoracic spine showing enhanced subarachnoid (arrow) and intramedullary lesions.

ratio of 40:30:30) with significant elevation of the protein level (623.9 mg/dL) and decreased glucose concentration (CSF 28 mg/dL; serum 105 mg/dL). Whole-spine radiotherapy was planned with 1.5 Gy/fraction to a total of 30 Gy; however, only a total of 16.5 Gy was administered because the patient presented with severe vertigo, confusion, disorientation, and hallucination. The radiotherapy did not effectively alleviate his pain, and his family refused further treatment; the patient died 2 months after diagnosis of spinal seeding.

3. Discussion

Symptomatic CSF seeding of intracranial GBM is rare, accounting for only 2% of cases in a study of 600 patients.[1] The same study showed that CSF seeding occurred mostly in the late stage of GBM, with a mean duration of 14.1 months after diagnosis of the primary tumor. CCRT and adjuvant TMZ has significantly prolonged the survival of GBM patients in recent years, although whether or not lengthier survival may lead to a greater chance of CSF seeding is still unknown. In the rare cases of spinal seeding reported, the time point of diagnosis was usually after intracranial tumor recurrence or progression, and most of these patients died from progression of the intracranial disease.[1–3] However, our case demonstrated that CSF seeding can occur when the primary tumor is well-controlled by radiotherapy and chemotherapy. In cases of tumors in close contact with CSF, young patients, or in which the ventricles were opened during surgery, there may be greater risk of metastasis into the CSF.[1] In the series of Bryan (1974),[4] 57 cases of GBM with intraventricular or spinal seeding were diagnosed at post mortem, and all of these tumors directly destroyed the ependymal lining and invaded the ventricles. Prophylactic craniospinal irradiation may be considered in patients at high risk of seeding.

The thoracic and lumbosacral spine are the most common sites for spinal seeding.[5] The seeding of tumor cells usually presents as a solid tumor rather than a layer of tumor coating the spinal cord or brainstem.[2,3] The common presentations of spinal seeding include back pain, radicular pain, paraparesis or quadraparesis, and urinary retention/incontinence.[6] If CSF seeding involves the brainstem, changes in mental state may be observed.[7]

CSF study is a useful tool if patients of GBM develop atypical symptoms during treatment or in the follow-up period.[8] The CSF finding of neoplastic cells or elevated protein levels may indicate MRI study of the whole spine with gadolinium contrast in order to evaluate the possibility and extent of spinal seeding.

Although the unmethylated promoter of MGMT in the primary tumor of our patient was not predictive of a good outcome,[9] the tumor was not in progression after CCRT and

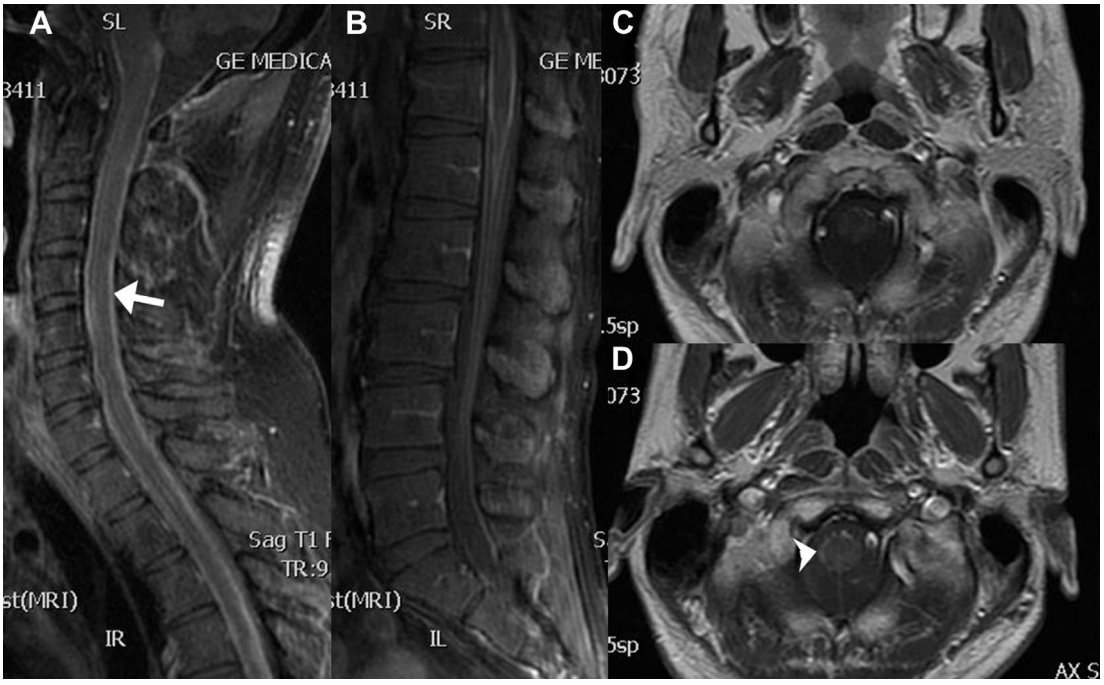

Figure 3 Postcontrast T1-weighted MR images of the cervical (A) and lumbar spine (B) demonstrating subarachnoid and leptomeningeal enhancement (arrow). Postcontrast axial T-weighted MR images of the brain taken upon patient presentation of back pain, showing an enhanced lesion (arrowhead) surrounding the medulla oblongata (D), which can be compared with images obtained after 5-month adjuvant chemotherapy (C).

7-month adjuvant chemotherapy. The methylation status of the tumor cells in the CSF was not determined owing to the insufficient number of tumor cells collected. CSF seeding has never previously been reported in cases in which the primary tumor appears to be controlled with radiotherapy and chemotherapy with no regrowth. A case of spinal cord intramedullary metastasis of GBM has been reported, but the patient had received only radiotherapy.[6] A difference in the level of expression of glial fibrillary acidic protein (GFAP) between the primary site of the tumor and the disseminated tumor indicates the possibility of genetic changes during the course of treatment,[8] and these genetic or epigenetic alterations may explain why the metastatic tumors are refractory to adjuvant temozolomide chemotherapy.

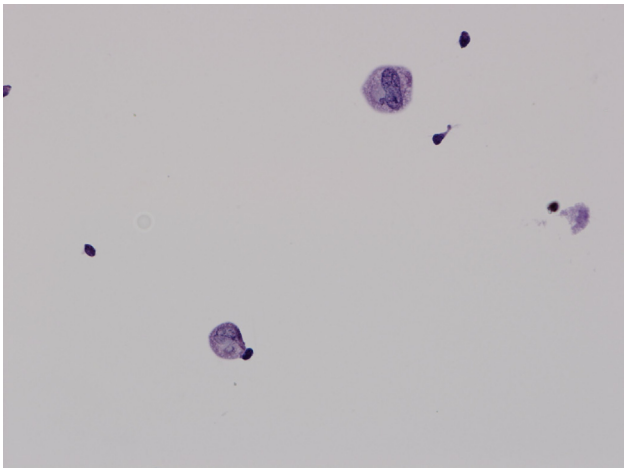

Figure 4 CSF cytology. A few atypical cells are apparent, with enlarged round to oval nuclei and abundant cytoplasm.

Survival after a diagnosis of leptomeningeal metastasis has been reported to be around 2—4 months.[1,8,10] Radiotherapy has been reported to temporarily control back pain caused by spinal seeding, but was not found to be of benefit in terms of survival.[1] To date, there is still no standard therapy for recurrent GBM after failure of radiotherapy and alkylator-based chemotherapy. For recurrent tumors, clinical trials of some new regimens have demonstrated some progression: A combination of anti-VEGF and topoisomerase 1 inhibitor in a Phase II clinical trial improved the prognosis for patients of recurrent GBM,[11] and other clinical trials focusing on single-agent or multi-agent chemotherapy have demonstrated some activity.[12—16] In our patient, administration of second-line chemotherapy with bevacizumab and irinotecan had been considered after the completion of whole-spine radiotherapy; however, the plan was cancelled because of the rapid deterioration in the patient's condition.

This case illustrates the importance of considering the possibility of CSF seeding when new symptoms occur even if the supratentorial GBM is stable after radiotherapy and chemotherapy. MRI should be used as an initial imaging study to evaluate suspected spinal dissemination. Radiotherapy and systemic or intrathecal second-line chemotherapy may help to alleviate the symptoms and prolong survival. We suggested that the prophylactic craniospinal irradiation may be considered in patients at high risk of seeding immediately after surgery.

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